

# ABUSE OF DRUGS

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## INTRODUCTION

Drug abuse may manifest at one of several different levels. Habituation involves a distinct and possibly harmful pattern of use. Drug abuse has been defined as a pattern of problem use that results in health consequences, social problems, or both. Drug addiction is a chronic disease of the brain that involves relapse, progressive development, and the potential for fatality if not treated. Addiction cannot be cured but can be brought into remission through a program of treatment, abstinence from all psychoactive substances, and supported recovery. In general, the drugs involved in abuse of drugs are within the grouping of “psychoactive” drugs. These are substances that have their primary effect on the brain and central nervous system (CNS) and include opioids, sedative–hypnotics, stimulants, and hallucinogens. Recent additions include performance-enhancing drugs, such as steroids, and combinations producing the effects of several drug groups.

## LEVEL OF DRUG USE AND ABUSE

Inaba and Cohen (1) list six levels of drug use and abuse. These are: 1) abstinence, 2) experimentation, 3) social/recreational, 4) habituation, 5) drug abuse, and 6) addiction. These levels may not be progressive from one to the next, but will indicate in a progression context if the individual is developing a drug problem.

### Abstinence

Abstinence means no use of psychoactive substances. However, in our culture, or for that matter in any culture, psychoactive substances are virtually impossible to avoid. Nearly all of us have experienced pain medication. Most soft drinks, tea, and, of course, coffee contain caffeine, a potent stimulant. Yet, individuals who partake of these will consider themselves abstinent and with few

exceptions this use is marginal to the point of not being worth consideration.

In terms of potential drug abuse or addiction, the nominally abstinent person is in little danger. Development of abuse requires the initial use of potent drugs. Addiction may involve a genetic vulnerability, but it also requires an environment that is conducive to initial use, and that will be lacking in the consistently abstinent individual, so long as he or she remains abstinent.

## Drug Experimentation

Experimentation usually ensues when the individual becomes curious about a drug's effects or is influenced to try a drug by relatives, friends, coworkers or such cues as advertising and word of mouth. Many young people in the late 1950s and early 1960s tried marijuana when it was offered to them. Although all they may have heard about the drug in school, from parents, teachers, and other authority figures was highly negative regarding the drug, they were curious as to its effects and that curiosity overrode the warnings that they had received.

Experimentation, however, involves no pattern of use and usually minimal negative consequences. The individual may use on occasion as the occasion presents itself, but there is no drug-seeking behavior, and the consequences are minimal. There are exceptions, however, and these may include:

- Using a large amount, such as binge drinking in high school or college under peer pressure, that results in accident, injury, or illness
- An extreme physical reaction to a small amount of drug via an allergy or idiosyncratic reaction
- Aggravation or triggering of a pre-existing physical or mental condition
- Use during pregnancy
- Use resulting in legal problems such as an arrest for possession or loss of a job after failing a drug test or
- An addictive response from individuals with a very high susceptibility to compulsive use triggering immediate abuse or addiction.

## Social or Recreational Use

With social or recreational use, the individual does seek out the drug or the situation in which the drug is used. However, there is no established pattern. Drug use is irregular, infrequent, and still has minimal impact on the individual's life. All of the possible exceptions listed in the preceding paragraph apply, with perhaps a greater chance given that drug-seeking behavior has become part of the pattern.

## Drug Habituation

A definite pattern of use is apparent in habituation. This category includes the individual who needs a cup of coffee to kick-start the day, or a martini on arriving home to relax and end the day. So long as no real harm to others or oneself is taking place, this sort of consistent drug use can be considered habituation. This is the point, however, where use is apt to slide over into abuse. Habituation indicates that the user has lost some control over the drug, that use has become a habit, and with a nudge could become a bad habit.

## Drug Abuse

Drug abuse can be transient: the product of stress, the acting out of social and cultural patterns, the response to overwhelming circumstances, or the need to perform. Examples may include taking a sedative to turn off and go to sleep after a hard day's work with a lot of mental but no physical exercise; doing cocaine or other stimulants to cope with a 24/7 lifestyle; having a weekly night out with the guys or staying over at the pub with coworkers on the way home; getting drunk to deal with a crisis one does not really want to face; or using steroids to bulk up for a professional sporting competition.

On the other hand, it can become chronic. Abuse behavior takes place on a regular basis, no matter what the circumstances. The behavior has become ingrained and part of the abuser's routine, such as the individual who must have a cigarette as soon as he or she wakes up in the morning, talks on the phone, and sits down to a meal, etc. As of yet, the problem is not addiction.

## Drug Addiction

Drug addiction is a disease of the brain that is characterized by compulsion, loss of control, and continued use despite adverse consequences. Inaba and Cohen (1) define compulsion as "H spent most of their time either using, getting, or thinking about the drug" as the step between abuse and addiction. Seymour and Smith (2) consider "loss of control" the pivotal point. In the

recovering community, that is the point where the user turns from a cucumber into a pickle.

Addictive disease is characterized by compulsive use of one or more drugs and loss of control over that use. Here, we have the individual who goes out, swears he or she will have no more than two beers and instead gets very drunk, has a blackout, and cannot remember getting home. Continued use despite adverse consequences can include the businessman who continues to use cocaine even after losing family, possessions, and business, or the person who smokes two to three packs of cigarettes a day despite having lung cancer.

Addiction is progressive and can be fatal if not treated. It is incurable in that the addict cannot go back to noncompulsive, non-out-of-control use. In the recovering community, it is said that a cucumber can continue to be a cucumber, but once it becomes a pickle, it cannot go back to being a cucumber. Although incurable, the disease can, however, be brought into remission via abstinence from all psychoactive substances and a program of supported recovery.

Abstinence on its own is not enough for the addict. Addiction is a function of the lower brain and cannot be controlled by force of will. Craving will wear down the addict's resolve and in an attempt to resist can create a rigidity known in the field as "white-knuckle sobriety," in which the abstinent addict is clinging so hard that it is like the driver with such a grip on the wheel that his or her knuckles are bloodless. That is no way to drive a car or to maintain recovery from addiction. Recovery for the addict is a lifelong undertaking and requires help (3).

## THE NATURE OF PSYCHOACTIVE DRUGS

Psychoactive drugs are substances that are chemically similar to chemicals that occur naturally in the human brain and act as neurotransmitters of information between brain cells. Because of the similarity, these chemicals are able to pass through the blood-brain barrier that exists to protect the brain from foreign materials. Once in the brain, all psychoactive drugs produce their effects by stimulating the release, inhibiting the release, blocking the reuptake, or imitating the brain's own neurotransmitters. Often, in such actions as producing pleasure, relief from pain or inhibitions, or anxiety, these drugs perform more rapidly and effectively than the endogenous substances. That is the primary appeal of these drugs. People use them because they work. They produce the desired results, at least for the short term.

## THE PSYCHOACTIVE DRUG CATEGORIES

With a few notable exceptions, the bulk of psychoactive drugs that are abused by human beings fall into four general categories. These categories are: 1) opioid/analgesic drugs; 2) sedative–hypnotic drugs; 3) stimulant drugs; and 4) hallucinogenic drugs. There are drugs of abuse that either fall outside these basic categories, such as ether and other general anesthetics and steroids, or are considered to have attributes of more than one category, and these include the stimulant hallucinogens. Although the effects of psychoactive drugs may vary, they do have several things in common:

- Their principle action is in the brain and CNS, and they are therefore also referred to in the literature as “CNS” drugs.
- They are able to cross the blood–brain barrier that usually protects the brain from foreign substances because they resemble chemicals that are indigenous to the brain.
- They all act by stimulating, depressing, or imitating neurotransmitters that are native to the human brain and
- They all produce some form of disinhibition euphoria while they are active in the brain. It is this disinhibition euphoria that tends to be the most alluring general quality of psychoactive drugs.

### Opioid Drugs

The narcotic/analgesic drugs have been used medically for pain relief and have been abused primarily for their ability to induce a state of euphoria and control pain. Historical accounts of opium extend to Assyrian depiction’s of goddesses with poppy pods growing out of their heads from around 4000 BC. Opium smoking became endemic in China in the 19th century after the British began exporting the drug from large holdings in India. In Britain, opium pills of 2–3 grains were easily available from apothecaries well into the 20th century. These and the tincture of opium, laudanum, are thought to have addicted many British writers and artists of the “romantic” and “pre-Raphaelite” periods. In the United States, opium and cocaine were often combined in patent medicine and tonics sold by traveling “snake-oil salesmen” in rural areas. The typical turn of the century opioid abuser was “a middle-aged, middle-class white woman with children.”

Natural opioids, that is, opioids extracted directly from opium include codeine—used for dental and other postoperative pain; laudanum, paregoric—a mild tincture of opium mixed with camphor and used primarily for

control of diarrhea; and morphine. Heroin is a partial synthetic that combines morphine and diacetyl acid. There are a number of synthetic opioids, including the highly powerful fentanyl (Sublimaze<sup>®</sup>), methadone—used in morphine and heroin addiction treatment, and such pain control mainstays as meperidine (Demerol<sup>®</sup>), hydromorphone (Dilaudid<sup>®</sup>), and oxycodone (Percodan<sup>®</sup>).

### Medical use of opioids

Both natural and synthetic opioids are now, as they have been throughout medical history, the primary means of providing relief from pain and anticipatory anxiety. Along with analgesia, they induce a corresponding state of well-being or euphoria and at high doses somnolence, sometimes referred to as twilight sleep. They can also provide a sense of being immune to the effects of environmental and psychic distress, what street users refer to as “being in the wicker basket.” Opioid drugs can also be effective in controlling diarrhea and coughing.

### How opioids work

The molecular structure of opioids is similar to that of certain neurotransmitters that occur naturally in the brain. Because of the similarities, these drugs are able to cross the blood–brain barrier and able to occupy receptor sites used by these neurotransmitters. The brain substances are called endorphins, which is short for endogenous morphines. The endorphins are what provide our natural pain control.

If we consider pain to be a signal that something is wrong, then endorphins are the internal means of mediating that signal. The subjective sequence is more or less as follows: Say you hit your thumb with a hammer. Intense pain. The brain receives the message, “Stop hitting yourself on the thumb with that hammer!” You jump around and yell a bit. It really hurts. After a while, however, you may still feel some surface pain from damaged thumb tissue, but the intense initial pain is gone. The endorphins that the pain released in the brain have attached to receptor sites that have disconnected the acute pain signal to your CNS, and even given you a little sense of euphoria.

### Nonmedical use and abuse

Opioid drugs provide a vastly amplified version of what the internal pain management messengers provide. Beyond that, the use of opioid drugs gives the addict access to the reinforcement reward system, normally reserved to reward the performance of species-specific survival behaviors. That access provides the user with an experience that the brain equates with profoundly important events like eating, drinking, and sex. As a

consequence, opioid use becomes an acquired drive state that permeates all aspects of human life. This quality makes these drugs prime candidates for nonmedical use and abuse. Nonmedical use often involves self-medication and can be a result of medical misprescribing. Chronic pain sufferers, for example, may seek out street opioids to provide ongoing relief in situations in which they have been underprescribed for pain medication.

Whether iatrogenic in nature or developed on the street within a drug subculture, addiction to opioid drugs can occur with any drug in this category. Street users generally gravitate toward morphine and heroin, available through illicit dealers. Middle-class addicts and health professionals find prescription opioids more available to them. However, that can change over time and with changes in user status and drug availability.

### Ingestion of opioids

Opioids may be taken orally in pill or liquid form, such as codeine or the many opioid-based prescription cough and diarrhea medications. They may be injected under the skin (skin popping), intramuscularly or intravenously. Injection has the added attraction of producing a “rush,” i.e., a relatively immediate drug reaction that has been described by users as being like a full body orgasm. Intravenous injection is said to produce the most intense rush. Given the expense and the frequent difficulty in obtaining opioids and the often low potency of street drugs, economy of delivery is often a consideration. Injection provides the least waste of drug in that the substance is introduced quickly into the bloodstream without previous evaporation or metabolism taking place. With higher potency heroin, however, smoking or “chasing the dragon” is often the choice. Smoking actually is the most rapid system for delivering opioids or any other drug to the brain, even faster than intravenous injection. Further, in light of AIDS, hepatitis C, and other illnesses that can be communicated by needle sharing, smoking is seen by users who can afford high-quality opioids as the safest use—and often seen by them as nonaddicting.

### Physical dependence

Opioid users are subject to the classic symptoms of physical dependence. These are increasing tolerance and the onset of physical withdrawal symptoms. Tolerance involves needing more of the drug as time passes to achieve the same desired results. Physical withdrawal can initiate within hours of the last use and consists of a cluster of flu-like symptoms. Withdrawal is mediated by neural pathways separate from those involving the reward system, causing withdrawal events to be perceived as life-threatening, and subsequent physiological and

psychological reactions often lead to renewed opioid use. Withdrawal can be a tremendous force for continuing use, often at any cost (4).

## Sedative–Hypnotic Drugs, Including Alcohol

Sedative–hypnotic drugs and anxiolytic drugs are CNS depressants that are used medically to reduce anxiety and/or induce sleep. They may also be used as anticonvulsants. Phenobarbital, for example, is often the maintenance drug of choice for seizure-prone individuals. In general, the sedative–hypnotic family of drugs includes alcohol, barbiturates, benzodiazepines, and such barbiturate-like drugs as chloral hydrate, glutethimide, meprobamate, and methaqualone.

### The history of sedative–hypnotic drugs in medicine

The history of sedative–hypnotic drugs is one of attempts to find a drug or family of drugs that produces the desired effects without the risk of dependence and debilitating or life-threatening side effects and overdoses. In the 19th century, anxiety and insomnia were treated with opiates, bromide salts, chloral hydrate (developed in 1869), paraldehyde (developed in 1882), and alcohol. Each of these substances had its problems. The bromides could cause chronic bromide poisoning; many patients refused to take alcohol; and chloral hydrate and paraldehyde had objectionable taste and smell. As a result, the development of barbiturates was hailed as a major breakthrough.

### Barbiturates

Barbiturates are all derived from barbituric acid, first obtained from uric acid and synthesized in Germany by Dr. Adolf van Baeyer in 1864. Conrad and Guthzeit synthesized the first barbiturate, 5,5-diethylbarbituric acid (barbital) in 1882. In 1903, Emile Fischer and Baron Josef von Mering introduced barbital into clinical medicine under the trade name Veronal<sup>®</sup>. Phenobarbital, which has remained the “model T” of barbiturates, first appeared on the market in 1912 as Luminal<sup>®</sup>. Unfortunately, intoxication with barbiturates is qualitatively similar to intoxication with alcohol and produced similar problems of abuse.

### Benzodiazepines

A family of CNS depressants that has gained wide acceptance and use in the medical community is the benzodiazepines. These drugs, also called the minor tranquilizers, have been developed over the past 30 years, starting with chlordiazepoxide (Librium<sup>®</sup>), quickly followed by diazepam (Valium<sup>®</sup>). Since then, a variety

of benzodiazepines has been synthesized, including alprazolam (Xanax<sup>®</sup>) and triazolam (Halcion<sup>®</sup>). Benzodiazepines may differ in duration of effects and specific indications, but they are all cross-tolerant and chemically similar.

### Major tranquilizers

Major tranquilizers like the phenothiazines, which include chlorpromazine (Thorazine<sup>®</sup>), are not usually subject to recreational-type abuse. Problems with these drugs most often involve misprescription or lack of understanding of their effects by health professionals. They are not considered to be addictive, and although a few deaths have been attributed to the ingestion of them at high doses, it is difficult to use them to commit suicide. The most notable problem with these drugs is the development of extrapyramidal symptoms, including facial and other abnormal movements of the head and neck, as well as such Parkinson syndrome-like symptoms as tremor at rest, rigidity, and shuffling walk.

### Alcohol

Although its systemically administered medical uses have been limited to the treatment of methanol and ethylene glycol poisoning, alcohol is an excellent solvent and is used as a vehicle in many pharmaceutical formulations. It is also used topically as a disinfectant and to reduce fever through evaporation. Medieval alchemists considered it to be the “elixir of life,” a title that has survived in certain European fruit brandies called collectively *eau de vie*.

Although some cultures have expressly forbidden the use of alcohol (particularly some but not all Muslim cultures), most peoples have embraced this drug, giving themselves permission to use it ceremonially and recreationally, at least in moderate quantities. At the same time, alcoholism or alcohol addiction is considered to be a worldwide problem, and most cultures invoke sanctions against behavior related to alcohol overuse, such as drunk driving.

As a recreational substance, alcohol is second only to caffeine in worldwide use and second only to tobacco in health costs from abuse. In recent years, the American public has received a mixed message on alcohol's health benefits and deficits. Wine is said to help protect “moderate” drinkers from heart disease, but at the same time, alcoholism is responsible for more substance-related deaths than all other psychoactive drugs combined, with the exception of tobacco. Although there are few pharmacotherapies for alcoholism and alcohol abuse, a multimillion dollar project has been funded at the University of California at San Francisco by Gallo Wine

and the state of California to study alcohol neurochemistry and, if possible, to develop a cure for alcoholism. Remission from alcohol addiction was the aim of a fellowship developed in the mid-1930s, Alcoholics Anonymous, which today has a worldwide membership numbered in the millions.

Alcohol is usually imbibed in liquid forms such as beer, wine, brandy, and hard liquor, etc. The type of alcohol commonly consumed is known as “ethanol.” It is rapidly and efficiently absorbed into the bloodstream from the stomach, small intestine, and colon. Recent studies have suggested that women have a more efficient absorption than men. In the bloodstream, alcohol is distributed to all parts of the body, including the fetus(es) of pregnant women. Alcohol is metabolized in the liver and converted to acetaldehyde by the action of alcohol dehydrogenase (ADH) and other oxidizing agents at a relatively constant rate.

### Adverse effects

The effects of sedative–hypnotic overdose or intoxication are similar for all drugs in this class. Ethanol acts as a classic sedative hypnotic drug, although the quality of sleep may be reduced by its ingestion. Intoxication works to decrease most mental and physical acuity, causing lapses in judgment, unsteady gait, slurred speech, slowed reactions, and mechanical difficulty. Blackouts, that is, continuing to function physically while being mentally disengaged, can occur as tissue dependence develops. Blackouts can be particularly dangerous in that users may forget how many pills they have taken and dose themselves into inadvertent overdoses. The degree of disinhibition euphoria can rapidly shift to dysphoria or even rage reactions with violent acting-out. In advanced stages, the intoxicated individual may pass out or, in extreme cases, lapse into a coma requiring emergency resuscitation. Acute intoxication to any sedative–hypnotic can be a life-threatening event.

### Chronic abuse

The effects of chronic abuse can include memory impairment and chronic cognitive and psychomotor impairment. Tolerance develops to these drugs as the liver becomes more efficient in processing these drugs; however, the potential for a fatal overdose remains the same for these drugs. That means, as the sedative–hypnotic abuser needs and uses more of the drug, he or she comes closer and closer to a potential fatal overdose. Further, as a user gets older, age-dependent tolerance also occurs, in that the effect of a sedative–hypnotic on a 50-yr-old can be 5–10 times stronger than the same dose on a 20-yr-old.

### Cross-tolerance and cross-dependence

Cross-tolerance means that tolerance to any sedative–hypnotic drug will extend to other drugs in the same class. Cross-dependency means that use of any drug in this class, or any opioid drug will enhance the effects and abusers may turn to other drugs in either category to either supplement their drugs of choice or stand in for them if they are not readily available.

### Synergy and its dangers

Synergism can occur when more than one depressant drug, including alcohol, is used at the same time. In combination, that can cause a much greater reaction than the simple sum of effects. The liver tends to be choosy about what it metabolizes first. For example, diazepam is considered a relatively safe drug from the standpoint of being difficult to overdose on. However, if alcohol and diazepam (Valium) are taken together, the liver becomes busy metabolizing the alcohol, and the diazepam passes through to the brain at full strength. The result can be blackouts—resulting in even more use if the individual is medicating and forgets having already taken his or her medication, and extreme respiratory depression. These synergistic effects result in more than 4000 deaths a year and almost 50,000 emergency room visits for adverse multiple drug reactions (1).

### How they work

Benzodiazepines, barbiturates, and alcohol act by stereospecifically binding to recently discovered receptors in the CNS. The effects of CNS-effective sedative–hypnotics have generally been linked to this complex, which also contains the receptor for  $\gamma$ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain and the chloride ion channel, through which chloride ions pass (5).

GABA receptors are the primary site of action for benzodiazepines in a highly complex process, but one that gives rise to the possibility of developing benzodiazepine agonists, antagonists, and inverse agonists. Benzodiazepine antagonists, such as RO15-1788 or flumazenil, may provide treatment options for both overdose and chronic abuse.

## The Nature of Stimulant Drugs

Beyond the obvious of being stimulants rather than depressants, CNS stimulants have some basic differences from the two preceding groups of psychoactive substances. Although CNS stimulants can produce addiction, their users do not develop a steadily increasing tolerance.

Instead, as “presynaptic” drugs, they exhaust the brain’s own supply of stimulant neurotransmitters within the sympathetic system. This results in a binge pattern of use in which the user is forced to stop intense use periodically when the drugs no longer produce their desired effects so that the brain can replenish its supply of sympathetic transmitters.

The most common stimulant drugs are caffeine and nicotine, and their use is virtually worldwide. In recent years, the deleterious effects of nicotine have come under increasing scrutiny, particularly in the United States, where it has been recognized that tobacco is responsible for at least 400,000 deaths per year. At the same time that nicotine is being increasingly censured, caffeine is enjoying what seems to be an ever-increasing popularity. Perhaps this is because with increasing public health attention to the dangers of both tobacco and alcohol, it is the one remaining CNS drug that most people feel okay about using. Coffee shops have become the social centers of our society, and the market is increasingly dominated by chains that provide a wide variety of coffee products.

### Caffeine

In general, coffee, tea, maté, Coca-Cola<sup>®</sup>, and other sodas are so ubiquitous that people rarely think of them as drugs. Aside from individuals who are hypersensitive to caffeine, the controversy continues on whether caffeine itself is harmful or helpful to the people who use it. There is no doubt that caffeine is a CNS drug. It is well known that many individuals are physically dependent on its daily use and will exhibit withdrawal symptoms, including headache and disorientation, if their use is abruptly stopped. On the other hand, aside from the spiraling cost of cappuccinos, it may be hard to specify adverse consequences to the use of caffeine.

Writers such as Andrew Weil, M.D. (6), in his germinal book *The Natural Mind*, often contend that indigenous psychoactive substances used within cultural boundaries enhance rather than endanger the lives of their users. Plant stimulants, such as khat in Africa and the Near East and coca leaf-chewing in the South American highlands, are the most often cited as providing vitamins missing in the regional meager diets and needed stimulation for the hardscrabble existence of their users.

In teaching courses on drug abuse treatment to health professionals who may have had no personal experience with drug use and have a hard time understanding the compulsion involved, Richard Seymour asks how many are habitual coffee drinkers. Most hands usually go up. He then says, “Think about how you feel if you can’t get your first cup of coffee in the morning and then multiply that. That’s how the compulsive stimulant drug user feels.”

### Other CNS stimulants

A drug similar in structure and effect to the amphetamines, methylphenidate (Ritalin<sup>®</sup>), and phenylpropanolamine, a stimulant vasoconstrictor that shows up in many cough and cold remedies, should also be mentioned. The most insidiously dangerous stimulant, nicotine as found in tobacco, is discussed briefly as well.

### Cocaine

Cocaine is derived from the coca leaf, which has been chewed for its stimulant qualities by dwellers in the South American highlands since prehistoric times. When Spanish conquistadors first encountered the Inca Empire of Peru, coca leaves were a means of exchange controlled by the emperor himself. It is something of a miracle that coca leaf-chewing was not imported to Europe along with tobacco use at that time. And cocaine was not medically extracted from the leaf until 1860. Once the strong stimulant was isolated, however, it came into multiple use throughout Euro-American culture. Cocaine formed the original basis for coca-cola and could be found by itself or in combination with opium in a variety of quasimedical elixirs and tonics. Its use was recommended for the treatment of asthma, hay fever, fatigue, and at least a dozen other ailments. Sigmund Freud made frequent use of it, both personally and in his practice, and was involved in what may have been the first case of iatrogenic cocaine addiction. The most common use by serious abusers was by injection. Often cocaine was injected in a combination with morphine or heroin, called a “speedball.” By the early years of the 20th century, cocaine abuse had become serious enough in the United States for that drug to be included with heroin in the 1914 Harrison Narcotic Act.

Today, cocaine appears in several forms: coca leaf, liquid, powdered cocaine hydrochloride, purified freebase, and crack and can be chewed, insufflated, or snorted into the nose, injected (with or without opioids), or smoked.

### Amphetamine and methamphetamine

Amphetamines are a 20th century development that first came into general medical use in the 1930s for a wide variety of medical conditions. During World War II, amphetamines were provided in large quantities to combat troops and bomber crews who had to stay awake and alert for long periods. After the war, production of these drugs remained high in most of the combatant countries, and they were readily prescribed by physicians for everything from depression to prefinals fatigue in college students. The first serious outbreaks of amphetamine abuse occurred in Japan, where stockpiles of the drug remained at the end of the

war, and in Sweden. Although some abuse had existed in the United States, the first postwar outbreak of stimulant abuse took the form of high-dose intravenous methamphetamine abuse between 1968 and 1969.

### Stimulant drug pharmacology

Unlike opioid drugs, which work by imitating the indigenous morphines (endorphins) and attaching directly to the endorphin receptor sites, stimulant drugs produce their effects by acting as sympathomimetic agents and thereby stimulating the release of sympathetic neurotransmitters in the brain. The normal function of these sympathetic agents is to implement our “fight-or-flight” response by constricting blood vessels (vasoconstriction), increasing pulse rate and heart rate, increasing temperature (hyperthermia), and in general increasing alertness and response. These energy agents are also directly connected with the brain’s reward/pleasure center; thus, the satisfaction from using stimulants can be intense. One professional ball player who was introduced to cocaine at the height of his career said that the feeling from the drug was the same feeling he got when an entire stadium was on its feet shouting his name.

### Nicotine

Tobacco, the primary source of nicotine, was used ceremonially in both pre- and post-Columbian America, imported to Europe where it was both embraced and reviled as a recreational drug, condemned by the court of James I of England, and today may be responsible for more than 400,000 deaths a year in the United States alone. Contrary to popular belief, although nicotine may help focus attention, it interferes with complex brain functions including access to long-term memory and the performing of multiple attention tasks.

Nicotine and the other ingredients in tobacco have been cited as causing a variety of fatal illnesses. A study by the Centers for Disease Control and Prevention (CDC) in 1991 listed the causes of death related to smoking with annual death toll as follows: (cardiovascular) heart disease, 150,000; stroke, 26,000; other, 24,000; (cancer) lung, 112,000; other, 31,000; (nonmalignant pulmonary disease) chronic obstructive pulmonary disease, 62,000; other, including pneumonia and influenza, 21,000; for a total of 426,000 fatalities a year directly attributable to tobacco. Further, the CDC points out that tobacco is also responsible for an annual death rate of 53,000 per year among nonsmokers affected by smoke in their immediate environment.

Pharmacologically, tolerance to tobacco develops quickly but once established, levels of smoking may remain about the same throughout one’s smoking career.

A withdrawal syndrome has been well established. Withdrawal symptoms may vary but can include craving for nicotine, irritability, frustration, anger, anxiety, depression, difficulty in concentrating, restlessness, and increased appetite. Although nicotine withdrawal is highly distressing and may continue for weeks, the compulsion to resume use may remain high for an extended period of time, and weight gain may be daunting, but it is not life threatening. However, detoxification can be an attenuated process of reversing neuronal adaptation to nicotine.

Although nicotine is also absorbed into the bloodstream through chewing and the use of snuff, inhaling cigarette smoke provides the most rapid brain access. Nicotine can also be absorbed through the skin, facilitating the use of skin patches. It is readily absorbed through the stomach, but first-pass digestion in the liver greatly decreases the amount reaching the brain from the stomach. Patients using nicotine gum are, therefore, now advised to mix the gum with saliva and lodge it between cheek and gum to facilitate absorption through the buccal mucosa.

Use of tobacco is bolstered by the positive reinforcement of producing euphoria and maintained by the negative of rapid-onset withdrawal symptoms as soon as nicotine levels decline below the brain's accustomed levels that are quickly relieved by the ingestion of nicotine.

### The effects of amphetamine/methamphetamine

Stimulants promote the release of the brain's energy chemicals. On the short term, this can result in increased wakefulness and alertness, giving the occasional or situational user a performance edge. It was that edge that led science writers in the late 1940s to laud amphetamines as a wonder drug. Unfortunately, these drugs also deplete the available energy chemicals, induce a drug-based paranoia, and trigger intense cravings for more of the drug. Cocaine, in particular, blocks the reuptake of energy chemicals by the brain cells in which they are usually stored, creating a cerebral chain reaction until the chemicals are metabolized.

### Prevention efforts

In keeping with their stimulant nature, cocaine and the stimulants produce a very rapid onset of abuse. Prevention efforts brought the slogan "Speed kills." Rock musician Frank Zappa filmed a TV commercial in which he said, "Kids, if you keep using speed you'll end up just like your parents."

The most effective amphetamine/methamphetamine prevention agent, however, proved to be the intravenous users themselves. These individuals tended to be walking, acting-out, negative advertisements of their drug. Anorexia

left them skeletal, whereas stimulant psychosis turned them into violent victims of delusional paranoia, a danger to themselves and others.

Although these efforts were effective to some extent, it became evident in the late 1960s that not only illicit manufacture of methamphetamine but the production and subsequent diversion of pharmaceutical psychoactive drugs were out of control, and the government and industry took steps to remedy the growing problem.

## Hallucinogens

Although opioids and sedative-hypnotic drugs evolved primarily as medical substances for dealing with physical and psychic pain, and stimulants developed as recreational and performance-enhancing substances, hallucinogens had their role primarily within the realms of religion and magic. Throughout prehistory, history, and on into our own century, hallucinogenic substances have been used, often depending on the degree of sophistication of the culture in which they are being used, as a means of establishing contact with the spirit world, the realm of the gods, or the deeper reaches of the human subconscious. Shamans have used plant and mineral hallucinogens, often within the context of highly complex ritual to establish a point of contact between their people and their people's deities, or at least the supernatural forces that may affect their individual and collective lives.

Ethnobotanists have classified hundreds of plant hallucinogens, the majority of these originating in the rainforests of South America. In this article, however, the focus is on the five categories of hallucinogens classified by Goodman and Gilman (7):

1. Lysergic acid diethylamide (LSD)-like drugs, including mescaline, psilocybin, and psilocin;
2. Drugs that probably are LSD-like, such as DMA, DOM, and DMT;
3. Drugs that probably are LSD-like and have other properties, such as MDMA, MDA, and other amphetamine derivatives;
4. Drugs that probably are not LSD-like, such as 5-hydroxytryptophan; and
5. Drugs that are not LSD-like, such as scopolamine and  $\delta$ -9-THC.

### The history and nature of hallucinogens

The Goodman and Gilman classification obviously uses LSD as the base measure of hallucinogens. This LSD centrality most likely relates to the status of that drug as the most widely discussed and the most notorious of hallucinogens.



Although LSD was a relatively recent discovery, dating from 1943 when Dr. Albert Hofmann, a chemist at Sandoz Laboratories in Basel, Switzerland, accidentally ingested a small quantity of a substance he had first synthesized in 1938, its most active component, ergotomine, had a long history as a psychoactive agent. Occurring naturally as a rye-grain mold, ergotomine was featured in mystic potions in the classical world. In the Middle Ages, when its applied use had been forgotten, the hallucinogenic effects of ergotomine contamination in the bread supplies of entire communities was blamed on witchcraft and demonic possession.

Western scientific interest in hallucinogens was rekindled in the 19th century by poets and anthropologists observing and then participating in ceremonial rites involving psychoactive substances in a variety of cultures. Mescaline, the active ingredient in the peyote cactus used by religious sects in Mexico and the U.S. Southwest, was isolated in 1856 and by the turn of the century was available for research by the likes of Sigmund Freud, William James, and Havelock Ellis. It was, however, the discovery of what Dr. Hofmann considered the most powerful psychic drug (LSD) that induced tremendous scientific and popular interest in hallucinogen research.

With the advent of LSD availability, perception of these drugs underwent a process of evolutionary models. The first of these models was the psychotomimetic. This treated the drug experience as a form of psychosis, permitting researchers to study psychotic symptoms in nonpsychotic subjects. The psychotomimetic model was followed, although not necessarily superseded, by the hallucinogenic model, which treated LSD and mescaline as tools for studying the mechanisms of perception, and the therapeutic model, which involved the use of these drugs in the treatment of alcoholism, other forms of addiction, and mental health problems. Finally, there came the psychedelic model, which maintained that under proper conditions, the drug experience would be one of enlightening and productive consciousness expansion. It was with the psychedelic model that the use of LSD and other hallucinogens spread from the laboratory into the community.

### Acute and chronic effects

The adverse effects of hallucinogens are generally divided between acute and chronic or long term. The acute effects, often referred to as “bad trips,” occur as direct negative results of hallucinogen ingestion and involve such elements as frightening images and thoughts, fear surrounding loss of control, and fear of losing one’s mind.

**Acute effects:** In 1967, David E. Smith, M.D., identified the adverse effects of hallucinogens as “largely psychological in nature,” and classified them as acute

toxicity, effects occurring during the use of the drug, or chronic after-effects (8). Although there have been some occurrences of physiological consequences, particularly with MDMA, these have been primarily of an idiosyncratic nature, although in most cases the adverse effects of these drugs still appear to be psychological in nature.

The acute toxic effects take many forms. Often individuals knowingly take a hallucinogenic drug and find themselves in a state of anxiety as the powerful hallucinogen begins to take effect. They were aware that they had taken a drug, but felt that they could not control its effects. This condition is similar to that of not being able to wake up from a threatening dream. Some users experience a bad trip and try to physically flee the situation, giving rise to potential physical danger. Others may become paranoid and suspicious of their companions or other individuals.

Not all acute toxicity is based on anxiety or loss of control. Some people taking hallucinogens display decided changes in cognition and demonstrate poor judgment. They may decide that they can fly, and jump out of a window. Some users are reported to have walked into the sea, feeling that they were “at one with the universe.” Such physical mishaps have been described within the acid culture as “being God, but tripping over the furniture.” Susceptibility to bad trips is not necessarily dose related but can depend on the experience, maturity and personality of the user, and “set and setting,” (i.e., the circumstances and the environment in which the trip takes place). Sometimes, the individual will complain of unpleasant symptoms while intoxicated and later speak in glowing terms of the experience. Negative psychological set and environmental setting are the most significant contributing factors to bad hallucinogenic trips (8).

Talkdowns of most acute toxicity reactions can be accomplished without medication or hospitalization. Paraprofessionals with psychedelic drug experience have been particularly effective at sites such as large rock concerts. In the talkdown approach, one should maintain a relaxed, conversational tone aimed at putting the individual at ease. Quick movements should be avoided. One should make the patient comfortable but not impede their freedom of movement. Let them walk around, stand, sit, or lie down. At times, such physical movement and activity may be enough to break the anxiety reaction. Gentle suggestion should be used to divert patients from any activity that seems to be adding to their agitation. Getting the individual’s mind off the frightening elements of a bad trip and onto positive elements is the key to the talkdown.

An understanding of the phases generally experienced in a hallucinogenic drug trip is most helpful, in treating acute reactions. After orally ingesting an average dose of

100–250 µg of LSD, the user experiences sympathomimetic, or stimulant responses, including elevated heart rate and respiration. Adverse reactions in this phase are primarily managed by reassurances that these are normal and expected effects of psychedelic drugs. This reassurance is usually sufficient to override a potentially frightening situation.

From the first to the sixth hour, visual imagery becomes vivid and may take on frightening content. The patient may have forgotten taking the drug, and given acute time distortion, may believe this effect will go on forever. Such fears can be dispelled by reminding the individual that these effects are drug-induced by suggesting alternative images and by distracting the individual from those images that are frightening.

In the later stages, philosophical insights and ideas predominate. Adverse experiences here are most frequently attributable to recurring unpleasant thoughts or feelings that can become overwhelming in their impact. The therapist can be most effective by being supportive and by suggesting new trains of thought.

The therapist's attitude toward hallucinogens and their use is very important. Empathy and self-confidence are essential. Anxiety and fear in the therapist will be perceived in an amplified manner by the client. Physical contact with the individual is often reassuring, but can be misinterpreted. Ideally, the therapist should rely on intuition rather than on preconceptions.

Wesson and Smith (9) noted that medication may be necessary and should be given either after the talkdown has failed or as a supplement to the talkdown process. During the first phase of intervention, oral administration of a sedative, such as 25 mg of chlorthalidopoxide (Librium) or 10 mg of diazepam (Valium), can have an important pharmacological and re-assuring effect.

During the second and third phases, a toxic psychosis or major break with reality may occur in which one can no longer communicate with the individual. If the individual begins acting in such a way as to be an immediate danger, antipsychotic drugs may be used. Only if the individual refuses oral medication and is out of behavioral control should antipsychotics be administered by injection. Haloperidol (Haldol) (2.0–4.0 mg administered intramuscularly every hour) is the current drug of choice. Any medication, however, should only be given by qualified personnel. If antipsychotic drugs are required, hospitalization is usually indicated. It has been found at the Haight Ashbury Free Clinics, however, that most bad acid trips can be handled on an outpatient basis by talkdown alone.

As soon as rapport and verbal contact are established, further medication is generally unnecessary. Occasionally, an individual fails to respond to the above regimen and

must be referred to an inpatient psychiatric facility. Such a decision must be weighed carefully, however, because transfer to a hospital itself may have an aggravating and threatening effect. Hospitalization should only be used as a last resort.

**Chronic hallucinogenic drug aftereffects:** These present situations wherein a condition that may be attributable to the ingestion of a toxic substance occurs or continues long after the metabolization of that substance. With the use of hallucinogens, four recognized chronic reactions have been reported: 1) prolonged psychotic reactions; 2) depression sufficiently severe so as to be life threatening; 3) flashbacks; and 4) exacerbation of pre-existing psychiatric illness. Recently, a fifth chronic reaction has been listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, posthallucinogen perceptual disorder (PHPD).

Some people who have taken many hallucinogenic drug trips, especially those who have had acute toxic reactions, show what appear to be serious long-term personality disruptions. These prolonged psychotic reactions have similarities to schizophrenic reactions and appear to occur most often in people with pre-existing psychological difficulties, such as primarily prepsychotic or psychotic personalities. Hallucinogenic drug-induced personality disorganization can be quite severe and prolonged. Appropriate treatment often requires antipsychotic medication and residential care in a mental health facility, followed by outpatient counseling.

At the Haight Ashbury Free Clinics, it has been noted that some of the clients self-medicated their hallucinogenic-precipitated psychotic episodes with amphetamines (10). Often, this self-medication with amphetamines resulted in the development of amphetamine abuse, followed by secondary heroin, barbiturate, or alcohol abuse patterns, to ameliorate the side effects of the amphetamines. Thus, in certain patients, chronic psychological problems induced by LSD and other hallucinogenic drugs led to complicated patterns of polydrug abuse that required additional treatment approaches (9).

**Flashbacks:** By far the most ubiquitous chronic reaction to hallucinogens is the flashback. Flashbacks are transient spontaneous occurrences of some aspect of the hallucinogenic drug effect after a period of normalcy that follows the original intoxication. This period of normalcy distinguishes flashbacks from prolonged psychotic reactions. Flashbacks may occur after a single ingestion of a psychedelic drug, but more commonly occur after multiple psychedelic drug ingestion.

Flashbacks are a symptom, not a specific disease entity. They may well have multiple causes, and many cases called flashbacks may have occurred although the

individual had never ingested a psychedelic drug. Some investigators have suggested that flashbacks may be attributable to a residue of the drug retained in the body and released into the brain at a later time. Although this is known to happen with phencyclidine (PCP) and drugs similar to it, there is no direct evidence of retention or prolonged storage of such psychedelics as LSD.

Individuals who have used psychedelic drugs several times a month have indicated that fleeting flashes of light and afterimage prolongation occurring in the periphery of vision commonly occur for days or weeks after ingestion. Active and chronic psychedelic drug users tend to accept these occurrences as part of the psychedelic experience, are unlikely to seek medical or psychiatric treatment, and frequently view them as "free trips." It is the inexperienced user and the individual who attaches a negative interpretation to these visual phenomena who are likely to be disturbed by them and seek medical or psychiatric help. Although emotional reactions to the flashback are generally contained within the period of the flashback itself, prolonged anxiety states or psychotic breaks have occurred after a frightening flashback. There is no record of flashback activity specifically attributable to hallucinogenic drug use occurring more than a year after the individual's last use of a psychedelic drug (10).

**Chronic consequences of hallucinogen use:** The long-term study of adverse hallucinogenic drug reactions has revealed the existence of low prevalence, but quite disabling chronic consequences of LSD use. Of particular concern is PHPD. With PHPD, individuals describe a persistent perceptual disorder that they describe as being like living in a bubble underwater. They also describe trails of light and images after moving their hands, and they often describe living in a purple haze. This perceptual disorder is aggravated by any psychoactive drug use, including alcohol and marijuana, and is distinguished from flashbacks, which are episodic rather than chronic phenomena. With PHPD, the individual often experiences anxiety, even panic, and becomes phobic and depressed. With PHPD sufferers, our experience has been that individuals do not have a disturbed psychiatric history before the onset of psychedelic drug use and that PHPD can occur even after a single dose.

With more severe, prolonged hallucinogen reactions, such as an LSD-precipitated schizophrenic reaction or severe depressive disorder, individuals almost always have a premorbid psychiatric history and require inpatient treatment. With the prolonged psychotic reactions, antipsychotic medication is required, and with the

prolonged depressive reactions, antidepressant medication is required. A major concern involves teenagers with depressive reactions to psychedelic drug use that may result in severe depression culminating in suicide.

With PHPD, drug-free recovery with supportive counseling is often adequate treatment, although recovery may take several months, and anti-anxiety medication may be needed to treat the secondary anxiety and panic disorder that develops when the individuals feel that they are irreversibly brain-damaged and will never see normally again.

**Other concerns with hallucinogen abuse:** There are many variations on the conditions addressed above, particularly with PCP, a mind-body disassociative drug that can act as a stimulant, a depressant, and a hallucinogen, depending on the dosage. These are discussed in another article on treatment and assessment. Suffice it to say, the etiology and pharmacology of hallucinogenic drugs is varied and involves a number of differing symptoms and sequelae.

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